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**APPLICATION NUMBER**

**21-109 (17-970/S-050)**

**Medical Review(s)**

## MEDICAL OFFICER REVIEW

Division of Metabolic and Endocrine Drug Products (HFD-510)

APPLICATION #: 21-109/S-000 APPLICATION TYPE: Commercial NDA

SPONSOR: AstraZeneca  
Pharmaceuticals  
LP PROPRIETARY NAME: Nolvadex™

CATEGORY OF DRUG: Antiestrogen  
GENERIC NAME: tamoxifen citrate

ROUTE: oral

MEDICAL REVIEWER: Dragos Roman, MD  
REVIEW DATE: 07-22-2002  
PDUFA DATE: 09-01-2002

### SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
02/28/2002	03/01/2002	Supplemental NDA- Submission of Pediatric Study Reports	

Document Date: RFI ATFD APPLICATIONS (if applicable)  
APPLICATION Type: Comments:  
IND

1) **Overview of Application/Review:** Tamoxifen citrate is a nonsteroidal antiestrogen for oral administration that displays a variety of estrogen antagonist and estrogen agonist-like pharmacologic effects in different human tissues. This submission is a one-year, open label, non-comparative clinical trial of tamoxifen citrate in 28 patients with McCune-Albright syndrome, a rare pediatric condition associated with gonadotropin-independent precocious puberty. A pharmacokinetic analysis of tamoxifen and its major metabolite were conducted during this clinical trial. This submission is in response to a Written Request issued by the Agency on April 5, 2000.

Tamoxifen citrate proved efficacious in suppressing many, but not all the signs and symptoms of precocious puberty in a heterogeneous group of patients with McCune-Albright syndrome at a daily dose of 20 mg. Understanding the true size of this favorable effect is hampered by limitations in trial design (the pre-study baseline data were collected retrospectively). The most important safety signal identified in this trial is a doubling of the mean uterine volume.

Despite its small size and design limitations, this clinical trial is the largest in patients with McCune –Albright Syndrome and precocious puberty. The labeling changes resulting from this clinical trial should be approved. The following additional safety information should be collected in a Phase 4 study: serial pelvic ultrasounds and eye exams (for the whole duration of intended therapy) and EKG's at steady-state drug levels. Consideration should be given to establishing a centralized registry that should capture all significant reproductive organ changes in girls with McCune-Albright Syndrome who receive tamoxifen.

**Recommended Regulatory Action: Approved**

**Signed:** \_\_\_\_\_ **Medical Reviewer:** Dragos Roman MD

**Date:** \_\_\_\_\_

**Medical Team Leader:** David Orloff MD

**Date:** \_\_\_\_\_

**APPEARS THIS WAY  
ON ORIGINAL**

Table of Contents .....	3
Executive Summary .....	4
A. Recommendation on Approvability/Additional Studies, and/or Risk Management Steps .....	4
B. Summary of Clinical Findings.....	5
B.1. Brief Overview of Clinical Program .....	5
B.2. Efficacy.....	5
B.3. Safety .....	8
B.4. Dosing.....	9
B.5. Special Populations.....	9
Clinical review .....	10
A. Introduction and Background.....	10
A.1. Tamoxifen citrate .....	10
A.2. McCune-Albright Syndrome and available therapies for the treatment of precocious puberty in MAS.....	10
A.3. Regulatory history .....	11
A.4. Foreign marketing history .....	11
B. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews .....	12
C. Human Pharmacokinetics and Pharmacodynamics.....	12
D. Description of Clinical Data and Sources .....	13
E. Clinical Review Methods .....	17
F. Integrated Review of Efficacy.....	19
F.1. Brief Statement of Conclusions .....	19
F.2. General Approach to Review of the Efficacy of the Drug.....	19
F.3. Detailed review of clinical trial.....	19
F.4. Efficacy Conclusions .....	61
G. Integrated Review of Safety.....	62
G.1. Brief Statement of Conclusions.....	62
G.2. Description of Patient Exposure.....	62
G.3. Methods and Specific Findings of Safety Review .....	62
G.4. Adequacy of Safety Testing .....	65
G.5. Summary of Critical Safety Findings and Limitations of Data.....	66
H. Dosing, Regimen, and Administration Issues .....	67
I. Use in Special Populations.....	67
J. Conclusions and Recommendations.....	68
K. Appendix: Bibliography.....	72

## **Executive Summary**

### **A. Recommendation on Approvability/Additional Studies, and/or Risk Management Steps**

Tamoxifen citrate showed efficacy in suppressing signs and symptoms of precocious puberty in patients with McCune-Albright syndrome (MAS) in a non-comparative, open-label, one-year trial at a daily dose of 20 mg. Although understanding the true size of this favorable effect may be hampered by limitations in the trial design (the pre-study baseline data were collected retrospectively), the efficacy and safety information collected by this clinical trial is larger than any clinical experience recorded in the medical literature in girls with MAS and precocious puberty. The labeling changes reflecting this body of information should be approved.

Treatment with tamoxifen citrate has been associated with a doubling of the mean uterine volume. The nature of this safety signal has not been elucidated and needs to be fully characterized due to the known carcinogenic risk associated with tamoxifen use in adults (uterine neoplasms). In order to enhance the safety profile of tamoxifen citrate in girls with MAS and precocious puberty the following Phase 4 recommendations are made:

- A sizable group of girls with MAS who receive tamoxifen treatment should be followed for the whole duration of intended therapy. Such a group can be similar in size to the cohort evaluated in the clinical study (a minimum of 20 evaluable patients). All patients should have pelvic ultrasounds performed every 6 months which should evaluate uterine size, endometrial/myometrial changes, and ovarian size/structure. Strong consideration should be given to a centralized registry that should capture all significant reproductive organ changes in all girls with MAS who receive tamoxifen.
- All patients enrolled in the Phase 4 study should be followed with annual eye exams which should evaluate the presence of ocular adverse events noted in adults receiving tamoxifen (such as corneal changes, cataracts, etc). This evaluation should continue for the whole duration of intended therapy.
- Most patients enrolled in the Phase 4 study should have EKG exams to rule out QT<sub>c</sub> prolongation. This evaluation should be done at steady-state tamoxifen serum levels.
- Strong consideration should be given to the development of a pediatric formulation.

## **B. Summary of Clinical Findings**

### **B.1. Brief Overview of Clinical Program**

Tamoxifen citrate (Nolvadex™) is a nonsteroidal antiestrogen for oral administration that displays a variety of estrogen antagonist and estrogen agonist-like pharmacologic effects in different human tissues. Tamoxifen has been approved in 1977 by the Food and Drug Administration for the treatment of metastatic breast cancer in postmenopausal women. It is currently approved for the treatment of metastatic breast cancer (in both premenopausal and postmenopausal women, as well as in men), breast cancer in postmenopausal women (adjuvant therapy), ductal carcinoma in situ, and for the reduction in breast cancer incidence in high risk women 35 years of age and older.

The current application contains a single, non-controlled, one-year, open-label, pediatric trial in 28 patients with McCune-Albright syndrome (MAS) and persistent precocious puberty manifested by signs of pubertal development, menses, and/or significantly advanced bone age. Twenty five patients completed a full year of tamoxifen treatment consisting in a 20 mg oral daily dose of the marketed tablet formulation. Since there was no control group, the patients served as their own controls (i.e. changes in efficacy measures during a pre-study “observational” period were compared against changes during the study period). The pre-study period was largely retrospective (after establishing patient eligibility, pre-study data were collected from medical records and interviews with patients’ parents/guardians; an unspecified number of patients had bone age radiographs collected prospectively when the retrospective data were of poor quality).

A pharmacokinetic analysis of serum levels of tamoxifen and its major metabolite N-desmethyltamoxifen is also included in this application. Both the pharmacokinetic and the clinical data were generated in response to a Written Request issued by the Agency on April 5, 2000 to AstraZeneca Pharmaceuticals, pursuant to section 505A of the Federal Food, Drug, and Cosmetic Act.

The potential indication supported by this clinical trial is the treatment of gonadotropin-independent precocious puberty in patients with MAS. It should be noted that there is no approved therapy for this indication.

### **B.2. Efficacy**

Tamoxifen citrate showed a favorable effect on most efficacy endpoints analyzed. Although the trial included a variety of primary and secondary endpoints, most of them evaluated the tamoxifen effect on three measures of efficacy: vaginal bleeding, bone age advancement, and height velocity.

### **B.2.1. Effect of tamoxifen citrate on vaginal bleeding**

Tamoxifen citrate has been associated with a mean 2-fold reduction in frequency of annualized vaginal bleeding episodes in the primary analysis, which included all 28 patients exposed to the drug. The mean duration of the vaginal bleeding episodes decreased from 2.96 days pre-treatment to 2.41 days on tamoxifen treatment. The individual data analysis supported the trend of the mean data, that is, most patients showed a reduction in the frequency of vaginal bleeding episodes during the trial. However, not all patients improved on treatment for this efficacy measure. For instance, two patients showed an increase in the frequency of vaginal bleeding episodes and two other patients who did not have vaginal bleeding during the pre-study period developed menses while on tamoxifen citrate. One patient dropped out of the trial because lack of efficacy.

A responder analysis evaluated the number of patients who showed a  $\geq 50\%$  reduction or cessation of vaginal bleeding episodes during the trial. 66.7% of the patients in the primary analysis showed a  $\geq 50\%$  reduction in vaginal bleeding episodes during the trial. 62% of patients exhibited cessation of bleeding over a six-month period of treatment and 33% had no bleeding over the whole duration of the trial in the primary analysis.

The results of a protocol-valid analysis were consistent with the primary analysis.

The overall favorable response to tamoxifen citrate in the reduction of vaginal bleeding episodes needs to be interpreted in the context of a non-comparative clinical trial with retrospective data collection.

### **B.2.2. Effects of tamoxifen citrate on bone age advancement**

Bone age advancement was measured by changes in the bone age rate of increase ( $\Delta$  bone age/ $\Delta$  chronological age for the period of interest). The primary analysis showed a reduction in the mean bone age rate of increase. This favorable response was detectable by 6-months of treatment and continued for the 12 months of the trial. When compared to the pre-study bone age rate of increase, the change in bone age rate of increase was statistically significant at the end of the trial ( $p=0.023$ ). Despite favorable changes in the mean bone age rate of increase, the individual changes were very heterogeneous.

The results of a protocol-valid analysis were consistent with the primary analysis.

The apparent benefits of tamoxifen citrate on the reduction of bone age advance took place in a trial with methodological limitations. For instance, in some patients, radiology reports were used instead of centralized X-ray reading. The pre-study data was collected mostly retrospectively and the duration of the pre-study period was uneven among patients (it ranged between 0.24 years and 2.52 years). Several patients could not be evaluated due to missing data.

### **B.2.3. Effects of tamoxifen citrate on growth rate**

Tamoxifen citrate therapy has been associated with a mean reduction in growth rate of 1.68 cm/year in the primary analysis. The growth rate Z-score (a standardized measure of growth rate across ages and sexes) decreased from a positive mean value during pre-study (faster than normal) to negative mean values after treatment (slower than normal). The growth rate change during the treatment period reached statistical significance when compared to the pre-study growth rate in the primary analysis ( $p=0.0046$ ).

The individual changes in growth rate Z-score showed improvement in 21 (80.7 %) patients and worsened during tamoxifen therapy in 5 (19.2%) patients. All recorded response failures occurred in patients with bone ages less than 7 years. The apparent favorable response in patients with advanced bone ages is confounded by the natural reduction in growth rate that accompanies late stages of puberty. A responder analysis in a subgroup of patients with growth rates in excess of 0.8 SD for normal chronological age identified 60 % responders in the primary analysis.

The results of a protocol-valid analysis were consistent with the primary analysis.

The overall favorable effect of tamoxifen citrate on the reduction of growth rate needs to be interpreted in the context of a non-comparative and retrospective clinical trial with a pre-study period which was uneven in duration among patients (as short as 0.21 years and as long as 2.65 years). In addition, the pre-study period was not equal in duration for bone age and height data collection, thus limiting the ability to integrate these two variables.

### **B.2.4. Limitations of the study**

Several factors limit the ability to draw firm conclusions about the efficacy of tamoxifen citrate in MAS patients with gonadotropin-independent precocious puberty. .

Trial design. The study is limited in numbers (28 patients enrolled, 25 completers). Since MAS is an exceedingly rare condition, this limitation is an objective one (in fact this is the largest clinical trial in patients with MAS to my knowledge). More important than the size of the study is the fact that the pre-study observational period stipulated by the Written Request was interpreted by the sponsor as retrospective. This, along with the fact that the duration of the pre-study period was uneven among patients and even for the same patient for bone age and height data, limits the scientific robustness of the study and makes the already imperfect comparator of the study (the pre-baseline data) even more imperfect. To this end, missing datapoints in some datasets (especially bone age) reduce further the already small number of evaluable patients.

Patient population/criteria for inclusion in the study. Patients with MAS display a remarkable degree of clinical heterogeneity which is due, among other things, to waxing

and waning gonadotropin-independent estrogen secretion. The broad definition of persistent precocious puberty criteria applied in this trial (patients could have either vaginal bleeding, or clinical signs of pubertal development, or advanced bone disease) adds an extra level of the heterogeneity to an already heterogeneous patient population. Indeed, this is confirmed by the widely variable pattern of serum estrogen levels noted during the study. All the above-mentioned facts, along with the rarity of the disease, make a therapeutic clinical trial in MAS patients a daunting task.

Duration of the study. The current study provides one year worth of data. Although data beyond one year of treatment is lacking at this point, MAS patients are likely to be treated for periods considerably longer than one year (likely > 5years).

Tanner data. Efficacy data on Tanner staging are missing. Due to a methodological error these data were collected but in a manner that was not interpretable.

An unresolved efficacy issue is the inconsistent clinical response in different efficacy endpoints in the same patient. Many patients in the trial improved in some signs/symptoms but not in all the signs/symptoms of precocious puberty. If different clinical endpoints have different sensitivities to tamoxifen and potentially different thresholds of therapeutic efficacy is not known.

In conclusion, tamoxifen citrate showed a favorable clinical response. It reduced the frequency of vaginal bleeding, the bone age advance, and the growth rate over one year of treatment in patients with MAS and very heterogeneous signs/symptoms of precocious puberty. Any efficacy inferences have to be interpreted in the restricting context of a non-comparative study with retrospective and uneven pre-study data collection.

Comparing the efficacy of tamoxifen citrate against other non-approved therapies, although extremely important, is impossible. This is due to the fact that the published data on other therapeutic agents are extremely limited. The only large case series published on the efficacy of the aromatase inhibitor testolactone in MAS patients (Feuillan et al, 1993) includes patients with different baseline characteristics, used different study design and analyzed somewhat different endpoints.

### **B.3. Safety**

The safety data generated by this trial is limited to patients treated for one year with tamoxifen at a dose of 20 mg daily. Three patients dropped out of the trial (none of the withdrawals was due to adverse events). Tamoxifen use over one year has not been associated with any deaths, any serious adverse events or even non-serious adverse events that can be attributed to the study drug. This statement is made in absence of a comparator.

The safety assessments performed during the clinical trial did not identify any of the adverse events that could have been predicted on the basis of the known adult safety profile of the drug. It is not clear though, how complete some of the assessments have

been for some safety parameters (for instance it is not known how many patients had eye exams).

An important safety signal is identified during the trial. The daily regimen of 20 mg of tamoxifen citrate is associated with a doubling in mean uterine size. This safety signal is incompletely understood and varies considerably among patients. The exact nature (endometrial vs. myometrial), the reversibility, and the long-term evolution of this sign are not known. This safety signal needs to be further explored and understood before tamoxifen citrate can be considered safe in patients with MAS and precocious puberty. Since tamoxifen is both an estrogen agonist and an estrogen antagonist, it is conceivable that, in addition to suppressing endogenous estrogen effects on the uterus when estrogens are secreted, it may continue to stimulate the uterine endometrium and/or myometrium during the intervals when endogenous estrogen secretion normalizes.

The safety of tamoxifen citrate in girls with MAS and precocious puberty has not been studied beyond one year of treatment and the long-term effects of tamoxifen therapy have not been established in this patient population.

#### **B.4. Dosing**

Although this clinical trial did not attempt to establish a minimally effective dose or a dose-range of efficacy, the 20 mg daily dose of tamoxifen citrate appears to be effective in MAS patients with a broad range of signs and symptoms of precocious puberty. Interestingly, the 20 mg dose shows efficacy despite a four-fold range in mg/kg dosing. (due to a wide range of individual weights, the daily dose was as high as 1.45 mg/kg in younger children and as low as 0.35 mg/kg in school age children).

It is not known if a different dose regimen may show better efficacy or a better safety profile. Individualization of the dose regimen based on the information generated by the PK study does not appear possible.

No unfavorable drug-drug interactions were identified in this trial but it should be kept in mind that this is a small study.

A pediatric formulation was not developed and is desirable for patients < 7 years of age who, in general, cannot swallow tablets. No information was presented on how the 20 mg tablet was administered to the younger patients during the trial.

#### **B.5. Special Populations**

This study included only pediatric patients less than 10 years of age, all females, as stipulated in the Written Request. The inclusion of boys with MAS would have been inappropriate since tamoxifen is an antiestrogen.

## **Clinical review**

### **A. Introduction and Background**

#### **A.1. Tamoxifen citrate**

Tamoxifen citrate (Nolvadex™) is a nonsteroidal antiestrogen for oral administration that displays a variety of estrogen antagonist and estrogen agonist-like pharmacologic effects in different human tissues. Tamoxifen has been approved in 1977 by the Food and Drug Administration for the treatment of metastatic breast cancer in postmenopausal women. The currently approved therapeutic indications for tamoxifen citrate are: metastatic breast cancer (in both premenopausal and postmenopausal women, as well as men), adjuvant treatment of breast cancer (postmenopausal women), ductal carcinoma in situ, and reduction in breast cancer incidence in high risk women (35 years and older).

The recommended approved dose of tamoxifen citrate is 20-40 mg/day, orally. Doses greater than 20 mg are to be given in divided doses (morning and evening).

The current Nolvadex™ label, Pediatric use section, states that the “safety and efficacy of Nolvadex in pediatric patients have not been established”.

The following warnings are listed in the Nolvadex™ labeling: hypercalcemia (in breast cancer patients with bone metastases), endometrial cancer (common to all estrogens, presumed to be related to the estrogen-like effect of tamoxifen on the uterus), non-malignant effects on the uterus (hyperplasia, polyps), endometriosis, uterine fibroids, ovarian cysts, thromboembolic effects (deep vein thrombosis, pulmonary embolism), stroke, liver adverse events (elevated enzymes, rarely cholestasis, fatty liver, hepatitis, hepatic necrosis), cataracts and other ocular disturbances.

The following precautions are listed in the Nolvadex™ labeling: decreases in platelet counts, leukopenia, rare pancytopenia.

#### **A.2. McCune-Albright Syndrome and available therapies for the treatment of precocious puberty in MAS**

McCune-Albright Syndrome (MAS) is a rare disorder characterized by the classic clinical triad of precocious puberty, polyostotic fibrous dysplasia, and cafe au lait spots. These symptoms can be fully present (classic form) or partially present (“forme fruste”). MAS is caused by an missense mutation in the gene coding for the stimulatory subunit of the G protein involved  $G_s\alpha$  which is involved in intracellular signalling. The altered  $G_s\alpha$  (which contains a substitution of arginine in coding amino acid 201 to a cysteine or histidine) causes autonomous activation of G-protein stimulated cAMP formation, a phenomenon known as “constitutive activation.” This mutation is a post-zygotic event which leads to a mosaic distribution of the affected endocrine and non-endocrine tissues. The resulting heterogeneity in clinical symptoms can be extreme. Gonadal manifestations of the disease consist in waxing and waning estrogen secretion by ovarian cysts. This

results in episodic uninhibited sex steroid production and subsequent sustained pubertal development in a subgroup of patients. Although initially independent of gonadotropin secretion, the MAS precocious puberty is followed by activation of the hypothalamus and a central (gonadotropin-dependent) component. Expression of the activating mutation in non-gonadal endocrine tissues may lead to hyperthyroidism, growth hormone excess, and Cushing's disease.

**Currently there are no drugs approved for the treatment of gonadotropin-independent precocious puberty in patients with McCune-Albright syndrome.** GnRH analogues can be used for the treatment of central precocious puberty when it further complicates the peripheral precocious puberty manifestations of MAS.

Several drugs, in different pharmacological classes have been used off label for the treatment of precocious puberty in patients with MAS. They include drugs that inhibit various steps in the estrogen biosynthetic pathway such as ketoconazole (Syed and Chalew, 1999) and aromatase inhibitors [in particular testolactone (Feuillan et al, 1986; Feuillan et al, 1993), and more recently anastrozole and letrozole]. Drugs that block estrogen activity at the level of the estrogen receptor, such as tamoxifen have been used successfully in small numbers of patients (Rodens et al, 1989; Eugster et al, 1999; DiMartino-Nardi, 2000; Eugster and Pescovitz, 2001). Medroxyprogesterone acetate has been used for control of menstrual bleeding but has no benefits in preventing skeletal growth and maturation.

### **A.3. Regulatory history**

The Division of Metabolic and Endocrine Drug Products issued a pediatric Written Request (WR) to Astra Zeneca Pharmaceuticals on April 5, 2000 to conduct a 1-year, open-label, multicenter, trial to evaluate the safety and efficacy of tamoxifen citrate in girls with MAS. The WR came at the end of a two year process (started on July 28, 1998) which included teleconferences and multiple communications between the sponsor and the Division of Metabolic and Endocrine Drug Products. On February 28, 2002, Astra Zeneca Pharmaceuticals submitted the pediatric study reports to the FDA as a Type 6 New Drug Application. The application contains a clinical study entitled "An open-label trial evaluating the safety and efficacy of Nolvadex™ (tamoxifen citrate) in the treatment of McCune-Albright Syndrome (Study 6157US/0013)". This study was conducted at 20 sites in the United States and includes 28 patients. It also contains a population pharmacokinetic analysis of tamoxifen nested into the clinical trial. Study 6157US/0013 is the subject of this review.

### **A.4. Foreign marketing history**

Nolvadex 10 mg Tablets were first approved in the United Kingdom on August 30, 1973, and in the United States on December 30, 1997. Nolvadex 10 mg Tablets are currently registered in one hundred and five countries worldwide.

Nolvadex 20 mg Tablets were first approved in the United Kingdom on January 29, 1982, and in the United States on March 21, 1994. Nolvadex 20 mg Tablets are currently registered in eighty-eight countries worldwide.

Nolvadex 30 mg Tablets and 40 mg Tablets are currently registered in four and ten countries worldwide respectively.

Nolvadex 10 mg Tablets have been withdrawn in eight countries. Nolvadex 20 mg Tablets have been withdrawn in seven countries. Nolvadex 30 mg and 40 mg Tablets have been withdrawn in three and ten countries, respectively. The sponsor states that "all of the above-referenced withdrawals have been made for local marketing reasons, none of which have been due to safety-related issues. Licenses have either been withdrawn, or allowed to lapse at the time of license renewal."

#### **B. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews**

No pharmacology and toxicology data were submitted with this NDA (i.e. no juvenile animal data). No such studies were asked in the Written Request.

#### **C. Human Pharmacokinetics and Pharmacodynamics**

The clinical trial 6157US/0013 included a population pharmacokinetic analysis of tamoxifen citrate and its active metabolite, N-desmethyltamoxifen. The data obtained from this pediatric analysis was compared with the known adult data.

The clinical pharmacology review establishes that the drug clearance in female children was approximately 2.3 fold higher than in adult female patients with breast cancer. The youngest cohort of female patients (ages 2 to 6 years) had the highest values for clearance (2.6 fold higher than adult patient values). Due to reduced body weight in these patients, the exposure to tamoxifen citrate was actually 3.5 fold higher than that observed in adult females after body weight adjustment. Exposure to the active metabolite, N-desmethyltamoxifen, was comparable between pediatric and adult patients.

The pharmacokinetic parameters of tamoxifen citrate in pediatric and adult patients are summarized in Table 1:

**Table 1: Age-related pharmacokinetics of tamoxifen citrate and N-desmethyltamoxifen**

Population pharmacokinetic Parameters	Pediatric Subjects (2 – 6 yr)	Pediatric Subjects (7 – 10.9 yr)	All Pediatric Subjects (2 – 10.9 yr)	Adult Subjects (43 – 75 yr)
Mean (SD)	N = 14	N = 13	N = 27	N = 59
<b>Parent drug</b>				
CL/F/kg (L/hr/kg)	0.262 (0.098)	0.192 (0.068)	0.227(0.090)	0.102(0.040)
V/F (L)	247(55.4)	277 (65.4)	261 (61.2)	438 (119)
C <sub>ssmax</sub> (ng/ml)	209 (73.0)	163 (73.0)	187 (64.4)	141 (44.7)
AUC <sub>0-∞</sub> (ng/mL)	4630 (1710)	3550 (1050)	4110 (1510)	3180 (1070)
t <sub>max</sub> (hr)	8.40 (1.32)	7.71 (0.744)	8.07 (1.12)	8.26 (1.41)
ka (hr <sup>-1</sup> )	1.18 (0.28)	1.24 (0.12)	1.21 (0.21)	1.27 (0.24)
t <sub>1/2</sub> (hr)	38.7 (14.7)	33.1 (9.07)	36.0 (12.4)	47.4 (17.3)
<b>N-desmethyltamoxifen</b>				
C <sub>ssmax</sub> (ng/mL)	359 (125)	319 (108)	340 (117)	339 (112)
AUC (t-tau) (ng.hr/mL)	7910 (2681)	6893 (2336)	7420 (2526)	7606 (2590)

#### D. Description of Clinical Data and Sources

##### D.1. Overall data and table listing of clinical trials

The data sources for this review consist primarily in a single clinical trial (trial 6157US/0013) submitted as supplemental NDA 21-109/S-000. The characteristics of this clinical study are summarized in Table 2, below.

**Table 2: Characteristics of Trial 6157US/0013**

Trial design	Patient population	Treatment	Duration of treatment	Primary end point	Secondary end points
Noncomparative, open-label, multicenter	28 girls aged 10 years or younger with classic or atypical McCune-Albright Syndrome with precocious puberty	Tamoxifen citrate 20 mg once daily	12 months	Clinical response	<p>Percent of patients meeting individual clinical criteria</p> <p>Frequency and duration of vaginal bleeding episodes</p> <p>Change in rate of increase in bone age</p> <p>Change in growth rate</p> <p>Change in predicted adult height</p> <p>Change in mean ovarian and uterine volume</p> <p>Change in Tanner staging</p> <p>Safety assessments</p>

## D.2. Postmarketing experience

There is no postmarketing experience with tamoxifen citrate in pediatric patients since this drug is not approved in pediatrics.

## D.3. Literature review

The sponsor references 3 publications of tamoxifen use in patients with MAS. They are listed chronologically below:

Rodens et al. "*Clinical, hormonal and sonographical characteristics of remission during treatment of pseudoprecocious puberty in the McCune-Albright syndrome*". *Acta Endocrinol* 1989; 120: 186-7. This abstract is the only comparison of tamoxifen against another drug (the aromatase inhibitor testolactone) in the treatment of precocious puberty in MAS patients. A 1.5 year-old girl with advanced bone age (2.5 years), accelerated height velocity (14.7-16 cm/year) and pubertal development (Tanner 2 breasts, and Tanner 1-2 pubic hair) received 5 mg tamoxifen for one year followed by testolactone at 100-200 mg/day. The two drugs appeared equivalent in reduction of height velocity, regression of Tanner staging, and were associated with a reduction in uterine volume. The recorded serum estrogen levels, although high before the beginning of the study were prepubertal at the infrequent times when they were measured during the study. There were no safety issues reported with either drug.

Eugster EA, et al: *Tamoxifen treatment of progressive precocious puberty in a patient with McCune Albright Syndrome*. *Pediatr Endocrinol Metab* 1999; 12: 681-686. This publication is a case report of a 4 and 9/12-year old African American female with MAS and progressive precocious puberty (growth velocity of 14 cm/year, breasts Tanner stage IV, bone age advanced to 10 years and vaginal bleeding present) who failed 13 months of testolactone and subsequently was treated with 10-20 mg of tamoxifen daily. During the treatment, the patient experienced cessation of menses, decreases in the rates of pubertal

progression and linear growth. The benefits lasted for three years of treatment without reported side effects. Although a single case report in a single patient, this is the longest published exposure to tamoxifen in MAS patients. There was no information provided on uterine size.

DiMartino-Nardi J. *Safety and efficacy of tamoxifen therapy in a two year girl with McCune-Albright syndrome*. The Endo Society 2000; 522: 2156. This brief abstract describes a 2 year-old female with MAS and precocious puberty (Tanner III breast development, Tanner II pubic hair), increased serum estradiol levels, accelerated growth velocity (16.4 cm/year), and advanced bone age (6 and 10/12 years) who was treated 10-20 mg daily for six months. On treatment, the patient had arrest of pubertal progression and bone age advancement with no clear change in growth velocity in the presence of increased serum estradiol levels.

In addition to the above mentioned MAS-related publications, the sponsor references 17 reports of tamoxifen use in children for non-MAS conditions. These conditions are: breast enlargement (pubertal gynecomastia, gigantomastia and virginal hyperplasia of the breast), proliferative fibroblast disorders (desmoid tumors, juvenile fibromatosis, retroperitoneal fibrosis), and malignant gliomas.

Four references (all case reports/series) summarize clinical observations related to the use of tamoxifen citrate in conditions associated with breast enlargement. One such study series describes briefly 14 adolescent males with pubertal gynecomastia who received uneventfully tamoxifen for 1-4 months with an apparent 86 % success rate and no identifiable safety concerns (Alagaratnam, 1987). Three other references (Morimoto et al, 1993; Baker et al, 2001; and O'Hare and Frieden, 2000) contain reports of tamoxifen use in juvenile gigantomastia. The reports present three patients, ages 12-17 years, who received 10-20 mg of amoxifen citrate daily for 1.8 to 6 months with overall clinical improvement. One patient experienced hot flushes, vaginal spotting, lower extremity edema and 100 lb weight gain after six months of therapy (unclear if drug-related).

Three publications reference the use of tamoxifen citrate in juvenile fibromatosis (Maddalozzo et al, 1993; Lackner et al, 1997; Ludemann et al 1999). One publication describes tamoxifen efficacy in a case of retroperitoneal fibrosis (Dedeoglu et al 2001). The basis of using tamoxifen citrate in these conditions is the observation that estrogen receptors are present in proliferating fibroblasts. Collectively, these studies describe six patients (3 boys and 3 girls, age range 11 months to 10 years) with tamoxifen exposures between two months and 4 years, at doses ranging between 10-20 mg/day. The good clinical response was associated with few safety issues. Two males of pre-schol age developed mild gynecomastia and one female patient developed ovarian cysts. The 30 mg dose was associated with liver enzyme elevation (ALT/AST, > 2XULN) which was reversible once the dose was decreased. Two patients who had "regular" liver enzymes, BUN, creatinine levels, and whole blood counts measured; these analytes were normal during the 12 months and 51 months of therapy, respectively.

Six referenced publications describe the use of tamoxifen citrate in patients with central nervous (CNS) malignancies (it is believed that tamoxifen has Protein Kinase C inhibitory activity). Three of them are case reports (Freeman A 1994; Ben-Arush MW 1999; Madden JR 2001) which do not described adverse events despite doses up to 60

mg/m<sup>2</sup> (a 13-year old girl experienced hot flushes and menstrual irregularities). The other three are clinical trials which are summarized below:

A pilot study of tamoxifen and carboplatin for children with low-grade gliomas (Walter AW et al 2000). This study enrolled fourteen patients (mean age 8.3 years) with a variety of gliomas. Patients received daily tamoxifen at 20 mg/ m<sup>2</sup> in conjunction with carboplatin. Tamoxifen administration was cyclical (12 weeks induction therapy followed by maintenance therapy for two weeks, with two weeks off-therapy periods for 12 planned cycles). The study provides limited interpretable safety data.

A study of high-dose tamoxifen for the treatment of refractory malignant gliomas of childhood (Pollack IF et al, 1997). In this Phase I study, 21 patients were treated with tamoxifen in two arms (60 mg/ m<sup>2</sup> and 100 mg/ m<sup>2</sup>). Most patients died due to progression of the underlying malignancy within 17 months of treatment. The authors do not report "any significant nausea or vomiting, evidence of thrombophlebitis, or neurotoxicity that was not otherwise attributable to the tumor". Two patients treated with the higher tamoxifen dose had asymptomatic prolongation of the QT interval which resolved after stopping the drug for two weeks and resuming therapy at a lower dose. PK serum levels for tamoxifen and its major metabolite (N-desmethyltamoxifen) were collected; they reached low micromolar ranges (5-15 µM) for the 100 mg/ m<sup>2</sup> treatment arm.

A Brazilian cooperative study of radiation therapy and high-dose tamoxifen in patients with diffuse brainstem gliomas (Broniscer A et al, 2000). In this one-year study, 29 patients (11 boys and 18 girls with a median age of 6.4 years) were exposed to high-dose tamoxifen (200 mg/ m<sup>2</sup>). Twelve patients received tamoxifen for a period longer of 6 months. Overall, the study failed to show significant clinical response. The most common or clinically relevant toxicities were: nausea and vomiting (mild to moderate), thrombosis (one patient), significant elevations in liver function tests (three patients had AST and/or ALT ≥ 70XULN with complete clinical recovery after tamoxifen discontinuation; one patient was rechallenged and liver toxicity recurred), possible seizure (difficult to interpret due the underlying CNS disease), multiple ovarian cysts at the end of treatment in two girls, ages 6 and 13 years (the massive size of the cysts necessitated surgical resection in one of these patients); "no significant endometrial changes were documented" (but not all patients had consistent ultrasonographic evaluation of the genital tract); mild increase in the mammary bud without any other signs of precocious puberty (4 patients); transient neutropenia (one patient). Eleven patients received treatment without experiencing any side effects. Ophthalmological toxicity was not identified but was incompletely assessed. In addition to clinical data this study included a PK study of tamoxifen and its major metabolite (N-desmethyltamoxifen). The serum tamoxifen levels were in the micromolar range (mean level of 2.44 µmol/L, range of 0.45 to 5.9 µmol/L). The mean N-desmethyltamoxifen steady-state serum level was 5.82 (µmol/L, range of 0.76 to 12.62 µmol/L).

The following observations can be made based on the review of the limited medical literature information on tamoxifen citrate use in pediatric patients.

The safety and efficacy findings reported with the use of tamoxifen in patients with MAS are in general consistent with the observations made in study 6157US/0013.

The safety data generated by high dose tamoxifen use in pediatric malignancies makes important contributions to the understanding of the safety profile of this drug in pediatric patients. The most important safety signals appear to be liver toxicity (associated with higher doses, reversible in all instances observed so far) and asymptomatic QT interval prolongation (dose-related). Additional potential safety signals are: nausea/vomiting, ovarian cyst formation, and mild breast development (in both boys and girls). Neurotoxicity was not clearly identified. Neutropenia and thromboembolic events, were present in a some studies but inconsistently and in extremely low numbers.

#### **D.4. Drug overdose information.**

The sponsor lists five cases of tamoxifen citrate overdose that have been previously reported in children. Three of these cases were reports of accidental overdose, and 2 cases were reports of intentional overdose.

One of the cases of accidental overdose was the granddaughter (age unknown) of a patient who accidentally took four 20-mg tablets of tamoxifen citrate. She had no reported adverse events. The other 2 cases were 3-year-old boys who accidentally ingested unspecified doses of tamoxifen citrate after they mistakenly received the drug when a prescription for amoxicillin was filled incorrectly. One of the boys experienced hyperagitation and developed a rash after receiving 2 doses of tamoxifen citrate. He was taken to a hospital emergency room, and vomiting was induced. No further details are available for the second boy, who had no reported adverse effects.

Two cases of intentional overdose were reported in teenage girls. A 16-year-old girl took an unspecified dose of tamoxifen citrate and other compounds in a suicide attempt and was hospitalized for psychiatric evaluation. A 13-year-old girl took 180 mg of tamoxifen citrate. There were no adverse effects reported for either girl.

Any firm conclusions derived from the tamoxifen overdose case reports are limited by the small number of patients involved and the lack of specific information describing the extent of the medical work-up.

#### **E. Clinical Review Methods**

This clinical review was conducted from the original paper and electronic data submitted in NDA21-109/S-000 (CDER stamp March 4, 2002), from the May 23/28 2002 and the June 18, 2002 response to information request. The indication to be studied is treatment of gonadotropin-independent precocious puberty in patients with MAS. The submission includes a single clinical trial and a tamoxifen PK analysis of all patients enrolled in the clinical trial. For the ease of the review, some of the submitted data were re-organized in new tables and figures. For each new table and figure an NDA source is specified. The submitted references regarding tamoxifen use in children were also reviewed.

The clinical trial design was as reviewed in details by the Agency prior to issuing the Written Request and met current ethical standards with respect to trial design. No placebo control arm was included since withholding treatment in patients with MAS and progressive precocious puberty would be unethical. The clinical trials appear to have been conducted in accordance to acceptable ethical standards. There were no DSI audits.

In response to financial disclosure requirements, the sponsor submitted FDA form 8454 which states that there was no financial agreement with the study investigators, that the study investigators had no proprietary interest or significant equity in the product, and that no listed investigator was the recipient of significant payments. One sub-investigator [redacted] received a sum greater than [redacted] from Astra-Zeneca for developing the clinical protocol. Dr. [redacted] contributed only one parent which was recruited, reportedly, by another investigator. Trial study 6157US/0013 was a multicenter study performed in 20 centers within the United States.

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## **F. Integrated Review of Efficacy**

### **F.1. Brief Statement of Conclusions**

Tamoxifen citrate showed efficacy in improving signs/ symptoms of precocious puberty in a very heterogeneous group of patients with MAS treated with 20 mg daily dose for one year. Tamoxifen reduced the frequency and the mean duration of vaginal bleeding episodes, reduced the mean bone age rate of increase of and the mean growth rate Z-score. Individual responses were very heterogeneous and not all patients improved on therapy. These findings should be added to the sponsor's proposed labeling which includes only the responder analysis information.

The sponsor's interpretation of the 6-month observational period stipulated by the Written Request as retrospective, limits the ability to draw firm conclusions on the efficacy of tamoxifen.

### **F.2. General Approach to Review of the Efficacy of the Drug**

This efficacy review is based on the submitted results of clinical trial 6157US/0013 which is reviewed in detail next.

### **F.3. Detailed review of clinical trial**

#### **F.3.I. Clinical trial description**

##### **F.3.I.1. Trial design and objectives**

Study 6157US/0013 is a Phase III clinical trial which evaluates the efficacy and safety of tamoxifen citrate in the treatment of precocious puberty in patients with McCune-Albright (MAS) syndrome. The trial was designed as a multicenter, non-comparative, open-label trial in patients diagnosed with MAS and progressive precocious puberty.

Twenty eight female patients with MAS  $\leq 10$  years of age were recruited at 20 institutions within the United States. After patient eligibility was determined, approximately 6 months of retrospective baseline information was obtained. Patients received 20 mg of tamoxifen citrate (one marketed tablet) daily for 12 months.

##### **F.3.I.2. Inclusion/exclusion criteria**

The main inclusion criteria were:  
Females ages 10 years or younger.  
Evidence of classic or atypical MAS.

Evidence of progressive precocious puberty, manifested by physical signs of pubertal development, episodes of vaginal bleeding, and/or significantly advanced bone age (>2SD above the mean).

Written informed consent provided by the parent/legal guardian.

The **exclusion criteria** included any single criterion of the following:

Previous treatment with tamoxifen citrate.

Liver function tests (ALT/AST)  $\geq$  3X upper limit of the reference range for age.

Previous drug therapy (excepting biphosphonates) for the treatment of MAS within the preceeding two months before trial enrollment.

The **withdrawal criteria** included progression of disease, loss of patients for follow-up, adverse events, significant concurrent illness, protocol noncompliance, withdrawal of consent, investigator's decision. Patients were to be followed for 30 days after the last dose of the trial.

The trial was conducted according to the **schedule of assessments** summarized below in Table 3.

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**Table 3: Schedule of assessments-trial 6157US/0013**

Visit	Screening <sup>a</sup>	Month 0	Month 3	Month 6	Month 12
Visit number	1	2	3	4	5
Informed consent	✓				
History	✓				
Physical examination (including height and weight)	✓		✓	✓	✓
Height and weight		✓			
Tanner staging	✓		✓	✓	✓
Clinical chemistry <sup>b</sup>	✓		✓	✓	✓
Pharmacokinetics <sup>c</sup>		✓	✓		
Hormone assays <sup>b,d</sup>	✓			✓	
Pelvic ultrasound <sup>e</sup> (uterus, ovaries)	✓			✓	✓
Bone age (x-ray)	✓			✓	✓
Slit-Lamp Exam					✓
Diary cards <sup>f</sup>	✓	✓	✓	✓	
Concomitant medications	✓	✓	✓	✓	✓
Adverse events			✓		✓
Dispense trial treatment <sup>g</sup>		✓	✓	✓	

<sup>a</sup> Screening assessments were to have been performed within 6 weeks prior to initiation of trial treatment, but after informed consent had been assigned.

<sup>b</sup> Laboratory tests were performed by an accredited facility. The time of day drug was taken and the time of phlebotomies was to have been recorded. Clinical chemistry included ALT and AST.

<sup>c</sup> First blood sample drawn 0-3 hours after first tamoxifen citrate dose, second blood sample drawn anytime 3 hours post initial dose and before second dose of tamoxifen citrate (e.g., 3-24 hours). Two additional steady state samples were randomly drawn anytime after 3 months on tamoxifen citrate therapy.

<sup>d</sup> Hormone assays included: serum estradiol, serum estrone, Dehydroepiandrosterone-sulfate (DHEA sulfate), and insulin-like growth factor-1 (IGF-1), and ultrasensitive (3<sup>rd</sup> generation) luteinizing hormone (LH) and follicle stimulating hormone (FSH).

<sup>e</sup> Pelvic ultrasound of ovary included length, width, height, and a description of cystic or solid component and size. Pelvic ultrasound of the uterus included dimensions and description of the uterine stripe.

<sup>f</sup> Diary cards included assessments of vaginal bleeding, vaginal discharge, and moodiness.

<sup>g</sup> Trial treatment started following patient number assignment by the AstraZeneca monitor or designee.

### F.3.I.3. Protocol amendments

The original protocol for study 6157US/0013 was submitted on February 15, 2000. The Written Request was issued on April 5, 2000. The sponsor amended the protocol twice: at the beginning of the trial (on May 10, 2000, submitted on July 7, 2000) and approximately halfway within the trial (on March 7, 2001, submitted on June 27, 2001). The first patient to receive tamoxifen did so on April 6, 2000 (all patients were started on tamoxifen during the year 2000). The last dose of tamoxifen was administered on October 30, 2001 (all patients but one completed the study in the year 2001).

The first protocol amendment (July 7, 2000 submission) contained the following changes:

- The age inclusion criterion was changed from < 10 years to ≤ 10 years (this change allowed a patient 10.9 years of age to be enrolled in the trial).
- The cessation of menses endpoint definition was changed from “no episodes during a 12-month period” to “no episodes during a 6-month period” (this change reduced the

stringency of the responder analysis, making a patient who improved during only a six month-period of the 12-month trial a responder for this endpoint; it was, however, consistent with the Written Request).

- The bone age advance endpoint definition was changed from a “reduction in bone age advance to <12 months during the 12-month trial period” to “a reduction in bone age advance to <6 during the 6-month trial period” (this change also reduced the stringency of the responder analysis, making a patient who improved during only a six month-period of the 12-month trial a responder for this endpoint; it was, however, consistent with the Written Request).
- Changed the growth velocity endpoint from a “reduction of growth velocity to +1SD for chronological age” to “reduction of growth velocity to the same as or less than 0.8 SD above the normal for chronological age” (this change was consistent with the Written Request).
- A change in the definition of a complete responder (consistent with the Written Request).
- Description of the time schedule for blood sampling for tamoxifen level determination (this change was consistent with the Written Request).
- Added of slit-lamp exam at the end of the trial to evaluate the presence of cataracts “if patient can cooperate” (consistent with the Written Request).
- Added of an interim analysis at six months of treatment statistical analysis (consistent with the Written Request).
- Clarifications concerning primary and secondary population analysis, statistical analysis methods (all consistent with the WR).

The second protocol amendment (June 27, 2001 submission) contained the following changes:

It allowed patients who completed the trial and responded to therapy to continue the treatment for an undetermined period of time;

Changed the definition of “significantly advanced bone age (>2SD about the mean)” to “significantly advanced bone age (>2SD about the mean) clarified to advanced bone age of at least 12 months beyond chronological age” (according to the sponsor this change was required by the methodology used by the \_\_\_\_\_ in reading the bone age radiographs which is based on criteria other than bone age standard deviation.

Overall, the protocol changes included in the two in the amendments harmonized the initial proposed clinical protocol with the April 5, 2000 Written Request. Other changes were minor and did not affect the trial design and analysis in any significant way.

#### **F.3.I.4. Primary endpoints**

The primary efficacy endpoints were the following:

- a) **Reduction of at least 50% in the number of menstrual bleeding episodes during the study period.** The terms “menses” and “menstrual bleeding” were replaced by “vaginal bleeding.” A vaginal bleeding episode was defined in this study as an

- interval of daily or intermittent vaginal bleeding which was followed by an interval of 14 days or longer during which time the patient had no vaginal bleeding.
- b) **Cessation of vaginal bleeding (no episodes in a six-month period).** The sponsor interpreted this criterion as no episodes of vaginal bleeding for either of the two six-month periods of the trial (Month 0 to Month 6 and Month 6 to Month 12).
  - c) **Reduction of bone age advancement to  $\leq 6$  months in a 6-month period.** The measure of bone age advancement was the bone age rate of increase. This was the ratio between the bone age change ( $\Delta BA$ ) for the time interval of interest and the chronological age change ( $\Delta CA$ ) for the same interval. Reduction of bone age advancement to  $\leq 6$  months in a 6-month period was interpreted by the sponsor that the rate of increase in bone age is less than or equal to the increase in chronological age in either 6-month period of the 12-month study (Month 0 to Month 6 and Month 6 to Month 12).
  - d) **Reduction of growth velocity to  $\leq 0.8$  standard deviation above normal for chronological age.** Growth velocity was defined as the increase in height divided by the length of the time period expressed as cm./year.

The primary endpoints were used in a responder analysis. A **complete responder** was defined as a patient who met successfully criteria (b), (c), and (d). A **partial responder** was defined as a patient who met successfully any one of the above criteria: (a) or (b) or (c) or (d).

#### **F.3.I.5. Secondary endpoints**

The secondary efficacy endpoints were the following:

- The change in the **frequency of vaginal bleeding** episodes from the pre-study period to the study period by patient.
- The change in the **average duration of vaginal bleeding** episodes from the pre-study period to the end of the 12-month study period by patient.
- The change in the **rate of increase in bone age** ( $\Delta BA / \Delta CA$ ) from the pre-study period to either 6-month interval during the study period.
- The change in the patient's **growth rate** from the pre-study period to the 12-month study period.
- The change in the **predicted adult height** from baseline to end of study for individual patients over the age of 6.
- The change in **Tanner staging** (as measure of pubertal progression) from baseline to end of study.
- The change in **mean ovarian volume** from baseline to end of study. The volume of each ovary was approximated by previously described methodology (Feuillan et al 1993).
- The change in **uterine volume** from baseline to end of study. Uterine volume was also approximated by previously described methodology (Feuillan et al 1993).

#### **F.3.I.6. Statistical analysis**

The efficacy data were analyzed for two patient populations: primary and protocol-valid. The **primary analysis population** consisted of all patients exposed to study treatment (i.e., all patients who received at least 1 dose of study medication). The **protocol-valid population** excluded the patients who had a protocol violations.

#### **F.3.I.7. Interim analysis**

An interim safety analysis for all treated patients and efficacy analysis for all patients who completed 6 months of trial therapy by 28 February 2001 was provided to the FDA in an interim report on 25 July 2001, Serial No. 007. (An erratum report was appended and submitted on 30 July 2001, Serial No. 009).

Of the 13 patients who were evaluated after 6 months of trial therapy, 2 were classified as complete responders, 9 were considered partial responders, and 2 patients were classified as non-responders at the 6 month interim time point.

#### **F.3.I.8. Clinical laboratory data**

Laboratory test results were assessed by examining individual values that crossed a threshold of significance. Laboratory data were summarized by patient for each trial visit. A central laboratory, \_\_\_\_\_ was used to process and analyze all blood samples.

#### **F.3.I.9. Withdrawals**

Three patients withdrew prematurely. None of the withdrawals were, reportedly, due to adverse events.

Patient 0025/0001 withdrew consent after 167 days of therapy (the reason for consent withdrawal is not mentioned).

Patient 0030/0004 was lost for follow up after her Month 3 visit (approximately 148 days into the trial). Since the date of the last dose is unknown, it was censored to the last visit.

Patient 0051/001 was withdrawn from trial treatment after 265 days (8 months) due to disease progression. This patient was withdrawn from the study after experiencing an increase in the number of vaginal bleeding episodes (from one episode during the 6-month pre-study period to 3 episodes during the first 6 months of tamoxifen citrate therapy).

#### **F.3.I.10. Protocol violations and major deviations**

A **protocol violation** was defined as any infringement of the protocol selection criteria. A

protocol deviation was defined as any departure from the protocol design or procedures after the patient had entered the trial. Table 4 lists the protocol violations and the major protocol deviations.

**Table 4: Protocol violations or major deviations potentially leading to exclusion from the protocol-valid population**

Center/ Patient No.	Violation or major deviation	Reason for exclusion	Protocol-valid population
	Tamoxifen citrate 20 mg qd		
0016/0001	Protocol violation	Received disallowed prior drug therapy	No
0025/0001	Major deviation	Duration of study treatment < 180 days	No
0030/0004	Major deviation	Duration of study treatment < 180 days	No
0031/0001 <sup>a</sup>	Protocol violation	Liver function tests (AST, ALT) ≥ 3x upper limit of reference range or missing	Yes

<sup>a</sup> This patient did not have liver function tests performed at screening. The patient is included in the protocol-valid population because subsequent liver function tests were within normal ranges.

ALT (SGPT) Alanine aminotransferase (serum glutamate pyruvate transaminase).

AST (SGOT) Aspartate aminotransferase (serum glutamic oxaloacetic transaminase).

qd Once daily.

Data were derived from Table G1.3.

Two protocol violations are reported:

- Patient 0016/0001 received Arimidex (anastrozole) prior to the beginning of the tamoxifen trial. The time period between the date of stopping Arimidex therapy to the screening visit was <2 months (exclusion criterion violation). However, if one takes into consideration the time that passed between the screening visit and the first day of tamoxifen citrate therapy, the patient had > 2 months off Arimidex therapy. The sponsor elected to exclude this patient from the protocol-valid population.
- Patient 0031/0001 was listed as a protocol violation because measurement of liver enzyme levels was not obtained at the screening visit. Measurement of ALT (SGPT) and AST (SGOT) levels at the next visit (Month 3) was within the normal range. The sponsor elected to include this patient in the protocol-valid population.

The following **protocol deviations** are reported:

Patient 0025/0001 withdrew consent following 167 days of study therapy.

Patient 0030/0004 was lost to follow-up after her Month 3 visit (approximately 148 days into the study trial).

One additional patient (0007/0001, not listed in the table) had tamoxifen citrate therapy discontinued for 47 days following the occurrence of significant nausea, moodiness, crying, and unhappiness during the first month of the trial. After the drug holiday the patient resumed tamoxifen therapy at 10 mg bid for 17 days. Since the patient's symptoms did not return during that time period, the patient resumed a dose of 20 mg qd to trial completion. Compliance for this patient was only 77% at the time of the 6 month interim analysis (protocol non-compliance). However, treatment compliance for this

patient at the completion of the study was 87% and she is no longer listed as a protocol deviation for this analysis.

On the basis of this interpretation the sponsor includes all 28 patients in the **primary safety and efficacy analysis** (i.e. "all patients exposed to study treatment) and 25 patients for the **protocol-valid population** (i.e. all patients exposed to study treatment who did not have a protocol violation or major deviation).

### F.3.II. Baseline patient characteristics

#### F.3.II.1. Signs and symptoms of McCune Albright syndrome

A summary of the common baseline signs and symptoms associated with McCune-Albright syndrome is presented in Table 5. It should be noted that only eight patients displayed the classic triad of café au lait spots, bone disorder, and precocious puberty (Tanner staging >2 or vaginal bleeding) at baseline. The vast majority of patients had atypical MAS. The diagnosis of MAS was made by the primary investigators and took into account several other pieces of information such as the patient's medical history, prior therapy, ovarian size and status, and estrogen levels. Inclusion of both typical and atypical MAS patients in the trial is in agreement with the Written Request.

**Table 5: Signs and symptoms of McCune Albright syndrome in patients enrolled in study 6157US/0013 (included are all patients exposed to study treatment)\***

Sign and symptom	Number and % of patients with each sign and symptom
Vaginal bleeding	24 (85.7%)
Accelerated bone age*	26 (92.9%)
Accelerated growth rate	15 (53.4 %)
Café au lait spots	15 (53.4 %)
Bone disorder	13 (46.4 %)
Advanced Tanner stage (≥2)	25 (89 %)

\*The MAS signs and symptoms were derived from past medical history including the pre-study period. \*\*Accelerated bone age was defined as a bone age to chronological age ratio of >1 at pre-baseline or at screening visit.

Source: Table 4

#### F.3.II.2. Prior therapies for MAS and associated conditions

Eleven (39.3%) patients had been previously treated for MAS and precocious puberty. Treatments included cyproterone, testolactone, medroxyprogesterone, anastrozole, tetrozole. Testolactone was the most frequently used medication for this purpose. Five patients (18%) had been diagnosed with central precocious puberty and were treated with leuprolide acetate (Lupron) prior to beginning tamoxifen citrate treatment in this study. However, only two were receiving Lupron at the beginning of the trial. Five (17.9%)

patients reported thyroid abnormalities. One patient (3.6%) reported growth hormone excess in her medical history but did not receive treatment for this condition until the follow-up period following her last dose of tamoxifen citrate.

### **F.3.II.3. Age**

Table 6 provides descriptive statistics for age at the time of informed consent. The mean age was 6.5 years; it ranged between 2.9 years and 10.9 years. Informed consent was obtained before the initial patient screening which, in turn, took place within six weeks prior to initiation of the trial treatment. Therefore, the actual ages at the beginning of the treatment may have been slightly higher than recorded in Table 6.

**Table 6: Age characteristics-primary population analysis**

Descriptive statistics (N=28)	Age
Mean	6.5 years
Median	6.9 years
Standard deviation	2.4 years
Minimum age	2.9 years
Maximum age	10.9 years

Source: T2.1. N=Number of patients.

### **F.3.II.4. Growth (bone age, bone age advancement, height, height velocity)**

The descriptive statistics for baseline growth-related parameters (bone age, rate of increase in bone age, height, and growth rate) are presented in Table 7. Due to incomplete data collection for some variables, the mean values are calculated from fewer than the 28 patients exposed to treatment.

The mean bone age at baseline was 9.1 years and ranged between 3.6 years and 12.5 years. It was calculated from 24 of the 28 patients enrolled.

The mean rate of increase in bone age during the pre-study period was 1.2 (advanced over chronological age). It was calculated for only 22 of the 28 patients. Characterization of the bone age characteristics at baseline is complicated by the fact that the length of baseline period of data collection was variable (as short as 0.24 years in patient 0018/0001 and as long as 2.52 years in patient 0033/0001).

The mean height Z-score was advanced for age and sex (1.21). The range of heights was wide (minimum height Z-score of -0.91 and maximum of 4.23). Baseline height data were available for all 28 patients enrolled in the study. The duration of the pre-study period for height was not the same for all the patients enrolled and did not always coincide with the duration of the pre-study bone age period for individual patients.

The mean growth rate during the pre-study period was 7.6 cm and displayed considerable variability between patients (the minimal growth rate was 2 cm/year and the maximal growth rate was 13.1 cm/year). The mean growth rate Z-score was advanced (1.3) but ranged considerably (from \_\_\_\_\_). Baseline growth rate data were available for all 28 patients enrolled in the study.

**Table 7: Baseline growth-related characteristics\***

Variable	Descriptive statistics					
	N	Mean	Median	SD	Min	Max
Bone age** (years)	24	9.1	9.71	2.25		
Rate of increase in bone age	22	1.2	1.4	0.79		
Height** (cm)	28	123.9	129.5	15.25		
Height** (Z-score)	28	1.21	0.99	1.27		
Growth rate (cm/year)	28	7.6	7.1	2.61		
Growth rate (Z-score)	28	1.3	1.0	2.72		
Weight (kg)	28	27.5	26.2	9.81		

Source: Table T2.2 and T5. N=number of patients.

\*Included are all patients exposed to study treatment for which baseline data were available.

\*\*For bone age, baseline measurement is time of screening. For height, baseline measurement is month 0.

### F.3.II.5. Vaginal bleeding

The number and duration of vaginal bleeding episodes during the pre-study period are displayed in Table 8 for 27 of the 28 patients enrolled (for one patient the selected definition of bleeding episode did not apply). The vaginal bleeding episodes show heterogeneity in both number and duration. The mean number of vaginal bleeding episodes was 1.8 (ranging from . \_\_\_\_\_). The mean duration of the vaginal bleeding episodes was 3 days (ranging from \_\_\_\_\_ days). The data was collected retrospectively for a six-month period in all patients.

**Table 8: Baseline vaginal bleeding characteristics \***

Vaginal bleeding episodes	Descriptive statistics					
	N	Mean	Median	SD	Min	Max
Number of episodes	27	1.8	1.0	1.65		
Average duration	27	3.0	3.0	3.22		

Source: Table T2.2 N=number of patients.

\*Included are all patients exposed to study treatment who met the applied definition of vaginal bleeding.

The distribution of patients with one or more episodes of vaginal bleeding during the pre-study period is summarized in Table 9. Most patients had more than one episode of vaginal bleeding. Seven patients (25.9%) had no evidence of vaginal bleeding at baseline. One patient (0045/0001, not listed in the table) had persistent bleeding and missing data and was not included in the analysis.

**Table 9: Distribution of patients with one or more episodes of vaginal bleeding**

Number of episodes of vaginal bleeding during the pre-study period	Number and % of patients with vaginal bleeding episode(s) N=27*
None	7 (25.9%)
1	8 (29.6%)
2	3 (11.1%)
3	4 (14.8%)
4	4 (14.8%)
5	0
6	1 (3.7%)

Source: Table G2.2

N=total number of patients.

\*Included are all patients exposed to study treatment who met the applied definition of vaginal bleeding (27).

The distribution of patients with various recorded durations of vaginal bleeding episodes during the pre-study period is described in Table 10. Most patients experienced vaginal bleeding episodes which lasted between one and five days. One patient (0045/0001, not listed in the table) did not meet the definition criterion for a vaginal bleeding episode and was not included in the analysis. Seven patients had no vaginal bleeding as a symptom at all.

**Table 10: Distribution of patients with various durations of vaginal bleeding**

Average duration of vaginal bleeding episode (days)	Number and % of patients with each duration of bleeding episode (N=27)*
No vaginal bleeding	7 (25.9%)
1 day	1 (3.7%)
2 days	4 (14.8%)
3 days	6 (22.2%)
4 days	5 (18.5%)
5 days	2 (7.4%)
≥ 6 days	2 (7.4%)

N=total number of patients.

\*Included are all patients exposed to study treatment who met the applied definition of vaginal bleeding (27).

Source: Table G2.2

### F.3.II.6. Tanner staging

Tanner staging showed considerable variability at baseline (Table 11). Three patients (10.7%) were Tanner I, eight patients (28.6%) were Tanner II, fourteen patients (50%) were Tanner III, two patients (7.1%) were Tanner IV, and one patient (3.6%) was Tanner V. The three patients who were described as being Tanner I at baseline were: 0015/0001,

0025/0001, and 0031/0001. It should be noted that, due to a deficiency in data collection, this information does not differentiate between Tanner staging for pubic hair and for breast development.

**Table 11: Baseline Tanner staging \***

Tanner staging	Patients (number and %)
Stage I	3 (10.7%)
Stage II	8 (28.6%)
Stage III	14 (50%)
Stage IV	2 (7.1%)
Stage V	1 (3.6%)

Source: Table G2.2

\*Included are all patients exposed to study treatment.

### **F.3.III. Efficacy Results**

#### **F.3.III.1. Primary endpoints**

The following primary endpoints are analyzed in this submission:

- Reduction of at least 50% in the number of vaginal bleeding episodes during the study period.
- Cessation of menses (no episodes in a six-month period).
- Reduction in bone age advancement to  $\leq 6$  months in a six-month period.
- Reduction of growth velocity to  $\leq 0.8$  standard deviation above normal for chronological age.

The sponsor conducted two types of analyses: a **primary analysis** for all 28 patients exposed to study treatment and a **protocol-valid analysis** for the 25 patients exposed to study treatment who, in sponsor's opinion "did not have a protocol violation or major deviation". Due to missing bone age data for several timepoints in different datasets, at the reviewer's request, the sponsor provided an additional analysis of a subset of patients for whom there was complete efficacy data available. For the purpose of this review this analysis will be labeled as **complete dataset analysis**.

#### **F.3.III.2. Summary of baseline data related to the primary efficacy endpoints.**

Baseline information for the efficacy endpoints analyzed (vaginal bleeding, bone age advancement, and growth rate) is summarized in Table 12:

**Table 12: Baseline characteristics for the primary efficacy endpoints \***

Variable	Descriptive statistics					
	N	Mean	Median	SD	Min	Max
Number of bleeding episodes	27	1.8	1.0	1.65	—	—
Average duration of bleeding	27	3.0	3.0	3.22	—	—
Bone age (years)	24	9.1	9.71	2.25	—	—
Rate of increase in bone age	22	1.2	1.4	0.79	—	—
Growth rate (cm/year)	28	7.6	7.1	2.61	—	—
Growth rate (Z-score)	28	1.3	1.0	2.72	—	—

Source: Table T2.2 and T5.N=number of patients.

\* Primary analysis population for which data were available.

Since trial US0013 is an uncontrolled trial, the efficacy analyses are comparisons between the pre-trial period and the on-study periods for various measures of efficacy. Therefore, full understanding of how baseline data were collected and how it impacts the clinical trial is critical. Several limitations of the pre-study period are listed:

- The collection of data during the pre-study period was largely retrospective. This is a major shortcoming of the study.
- The duration for the data collection during the pre-study period is not even among all patients in the trial. This is the case for both bone age and growth rate data.
- The duration of the pre-study period is different in individual patients for the rate of increase in bone age and for the growth rate, thus making difficult to integrate these efficacy variables.
- Datapoints at different times are missing, thus reducing the number of patients for which data can be analyzed. This statement applies primarily to bone age data and to rate of increase in bone age data which is calculated from the former.

Table 13 displays the duration of the pre-study period for the primary endpoints. It illustrates the uneven duration of the baseline period for bone age and height-related endpoints (highlighted are pre-study periods shorter than six months for individual patients). For instance, the pre-study period for height was as short a 0.21 years (patient 0051/0001) and as long as 2.65 years (patient 0052/0001). Five patients had pre-study observation period shorter than 0.46 years (0.21, 0.33, 0.38, 0.39, and 0.46 respectively). For bone age data, the pre-study period was as short as 0.24 years and as long as 2.52 years. The duration of the baseline bone age observation period also varied considerably among patients. The mean duration of the bone age observation period was 0.75 years (ranging from 0.24 years in patient 0018/0001 to 2.52 years in patient 0033/0001). Seven patients had bone age observation periods less or equal than 0.46 years (0.24, 0.31, 0.34, 0.36, 0.41, 0.44, and 0.46 respectively).

It should be pointed out that the pre-study observation period was not equal for bone age data and for height data in the same patient, thus limiting the ability to integrate these two variables.

While all 28 patients had baseline height measurements and therefore baseline growth rates, only 22 out of 28 patients had baseline measurement in  $\Delta$ BA/ $\Delta$ CA (three missed BA measurements at baseline, two missed at pre-baseline, one at both pre-baseline and baseline). Only 27 of the 28 patients could be evaluated for the number of baseline vaginal bleeding episodes (one patient had “continuous intermittent bleeding”).

**Table 13: Duration of pre-study data collection period for each endpoint**

Center/Patient number	Duration of observation period (fractional years)		
	Height (pre-baseline to Month 0)	Bone age (pre-baseline to screening)	Vaginal bleeding
0004/0001	0.49	0.31	0.5
0005/0001	0.61	NA/p	0.5
0005/0002	0.48	0.69	0.5
0005/0003	0.95	NA/b	0.5
0007/0001	0.46	0.44	0.5
0007/0002	0.49	NA/b	0.5
0009/0001	0.33	0.34	0.5
0010/0001	0.57	0.55	0.5
0012/0001	0.38	0.63	0.5
0013/0001	0.67	0.63	0.5
0015/0001	0.69	NA/p	0.5
0015/0002	0.79	1.23	0.5
0016/0001	1.11	0.36	0.5
0018/0001	0.95	0.24	0.5
0018/0002	1.13	0.41	0.5
0023/0001	0.49	0.49	0.5
0025/0001	0.39	NA/p/b	0.5
0026/0001	0.8	1.56	0.5
0028/0001	0.52	0.46	0.5
0030/0001	0.57	0.54	0.5
0030/0002	1.01	1	0.5
0030/0003	0.6	0.59	0.5
0030/0004	1.03	1.19	0.5
0031/0001	0.74	0.79	0.5
0033/0001	0.8	2.52	0.5
0045/0001	1.61	1.44	0.5
0051/0001	0.21	NA/b	0.5
0052/0001	2.65	0.63	0.5

Source: Table G10.1 for height data and G2.3 for bone age data. Highlighted are pre-study periods shorter than six months for individual patients.

NA/b= bone age radiograph not available at baseline; NA/p= bone age radiograph not available at pre-baseline; NA/p/b= bone age radiograph not available at pre-baseline and baseline;

### **F.3.III.3. Reduction and/or cessation of vaginal bleeding**

A vaginal bleeding episode was defined as an interval of daily or intermittent vaginal bleeding followed by an interval, 14 days or longer, during which the patient had no vaginal bleeding. "Cessation of vaginal bleeding" for a six-month period was interpreted that the patient had no vaginal bleeding episodes for either one of the two six-months periods (Month 0 to Month 6 or Month 6 to Month 12). Thus, a patient could have bleeding cessation for six months, experience bleeding for the next six months and still be considered to have "complete cessation of vaginal bleeding".

The pre-study data were collected retrospectively from interviews with patients' parents/guardians.

Table 14 summarizes the annualized frequency of vaginal bleeding episodes during the pre-study and the study periods for the primary analysis population and the protocol-valid population. Out of 28 patients enrolled, only 27 patients could have on-study to pre-study comparisons. For one patient (0045/0001) the pre-defined definition of vaginal bleeding episode did not apply; in addition, this patient had missing vaginal bleeding data for a significant period of the trial (over 165 days).

The primary analysis reveals a two-fold reduction in the mean number of vaginal bleeding episodes (from 3.56 pre-study to 1.73 on-study). The reduction in mean number of vaginal bleeding episodes for the protocol-valid analysis was similar (2.4-fold). There was an associated reduction in the maximal duration of the vaginal bleeding episodes for both types of analyses (from 12 days to 9.73 days in the primary analysis and from 12 days to 6.79 days in the protocol-valid analysis, respectively). It should be noted that the denominators are different for the pre-study and the on-study period since two patients dropped out. For missing diary data the number of episodes were calculated under a "worse case scenario" which assumed that vaginal bleeding occurred on days with missing data..

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**Table 14: Frequency of vaginal bleeding episodes for primary analysis population and protocol-valid population**

Population Analyzed	Tamoxifen citrate 20 mg qd (N = 28)				
	Parameter assessed <sup>a</sup>	n	Mean (SD)	Median	Range
<b>Primary analysis population (N = 28)</b>					
	Frequency pre-study (number of episodes per prior 6 months, annualized)	27	3.56 (3.30)	2	
	Frequency during treatment (number of episodes during 12 months, annualized)	27	1.73 (2.35)	1	
<b>Protocol-valid population (N = 25)</b>					
	Frequency pre-study (number of episodes per prior 6 months, annualized)	24	3.25 (3.33)	2	
	Frequency during treatment (number of episodes during 12 months, annualized)	24	1.33 (1.79)	0.5	

<sup>a</sup> Frequency during study treatment was calculated under the worst case scenario (assuming that bleeding occurred on days for which there was no diary data). Data were derived from Table T7.1. and T7.2.

Not all patients had vaginal bleeding during the 6-month pre-study period. Indeed, only 21 of the 28 patients had episodes of vaginal bleeding at baseline. There were 48 episodes of vaginal bleeding at baseline (annualized to 96) in 28 patients. There were 28 actual episodes of vaginal bleeding during the one-year trial and 38 episodes under a "worse case scenario" which assigns bleeding episodes during missing diary days. Fewer patients had vaginal bleeding on-study (14) than pre-study (21).

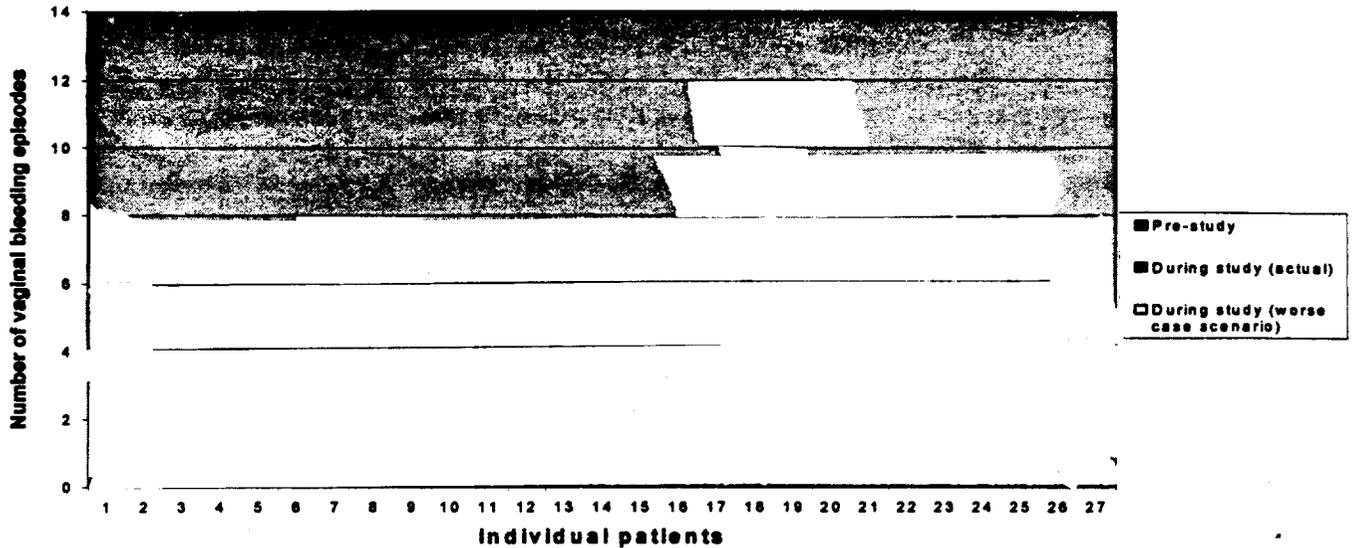
It is important to notice that not all patients showed an improvement in the frequency of vaginal bleeding during the trial. Of the seven patients who did not have vaginal bleeding episodes in the pre-study period, two patients (0007/0002 and 0031/0001) experienced three and one vaginal bleeding episode, respectively, while on tamoxifen citrate. Of the patients who experienced vaginal bleeding prior to the beginning of the study drug, two patients (0018/0001 and 0051/0001) experienced an increase of annualized vaginal bleeding episodes (2 episodes pre-study and 3 episodes on-study for patient 0018/0001, and 2 episodes pre-study and 5 episodes on-study for patient 0051/0001). While the former completed the study, the latter discontinued the treatment due to lack of efficacy.

Individual patient responses to tamoxifen citrate therapy are presented in Figure 1, which depicts the annualized number of vaginal bleeding episodes during the pre-study and on-study periods. The on-study period is represented by both actual number of vaginal bleeding episodes and "under the worse case scenario" number of vaginal bleeding episodes. Although individual responses were variable, the overall trend was toward

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reduction of menses during the trial when compared to the baseline period. It should be noted that some patients did not have vaginal bleeding during either or both periods.

**Figure 1: Annualized Number of Episodes of Vaginal Bleeding: Pre-study to On-study Comparison**



The reduction in the frequency of episodes of vaginal bleeding was associated with a reduction in the mean duration from 2.96 days pre-study to 2.41 days on-study (primary analysis population). The average duration of bleeding episodes decreased in 12 (57.1%) of the 21 patients in the primary analysis population that had vaginal bleeding pre-study and in 9 (50%) of the 18 patients in the protocol-valid population. The impact of missing diary data on these statements is not known (six patients had missing information for 1, 2, 10, 84, 87, and 161 days, respectively).

The sponsor conducted a **responder analysis** for two endpoints related to the frequency of vaginal bleeding (both were primary endpoints):

- Reduction of at least 50 % in the number of vaginal bleeding episodes from the pre-study period to the study period
- Complete cessation of vaginal bleeding in a 6-month period while on study medication.

These responder analyses focus on a subgroup of patients who had vaginal bleeding during the pre-study period. Both responder analyses were conducted under a “worse case scenario” for the missing data.

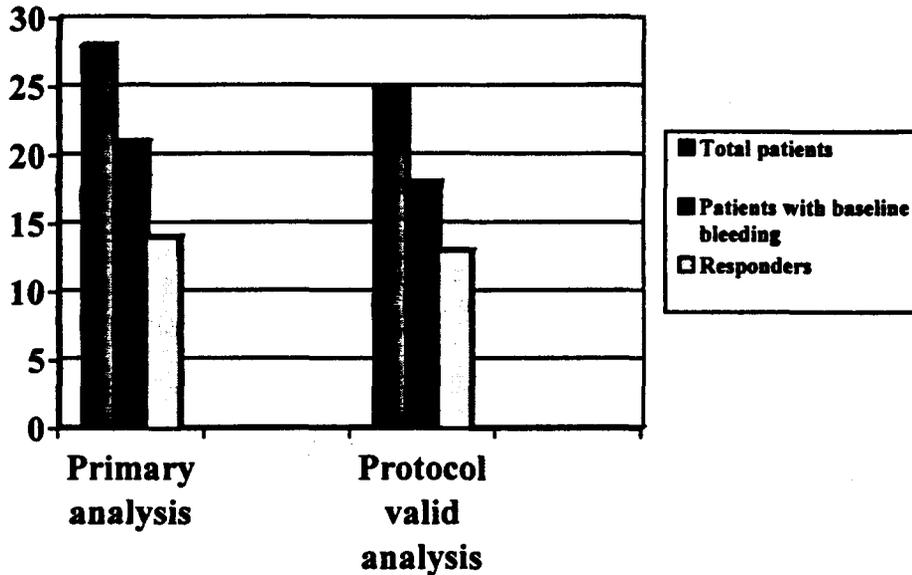
**≥ 50% reduction in vaginal bleeding episodes on treatment**

Of the 28 patients who were treated with tamoxifen citrate, only 21 (75%) exhibited evidence of vaginal bleeding during the six-month observation period. Of these, 14

patients (66.7%) experienced a  $\geq 50\%$  reduction in the frequency of vaginal bleeding episodes.

Of the 25 protocol-valid patients who were treated with tamoxifen citrate, only 18 (72%) exhibited evidence of vaginal bleeding at baseline. Of these, 13 patients (72%) experienced a  $\geq 50\%$  reduction in the frequency of vaginal bleeding episodes. This information is displayed in table #:

**Figure 2: Number of patients who had a  $\geq 50\%$  reduction in vaginal bleeding episodes on treatment**



#### **Complete cessation of vaginal bleeding**

“Cessation of vaginal bleeding”, as defined by the Written Request meant that the patient had no vaginal bleeding in a six-month period. The sponsor interpreted this as absence of vaginal bleeding in either six month-period during the 12 months of treatment (Month 0 to Month 6, or Month 6 to Month 12). According to this interpretation, a patient could have vaginal bleeding cessation for six months, experience bleeding for the next six months and still be considered to have “complete cessation of vaginal bleeding”. Therefore, in addition to the sponsor’s analysis this reviewer added an analysis which evaluates vaginal bleeding cessation for the whole duration of the trial.

Of the 28 patients who were treated with tamoxifen citrate, only 21 (75%) exhibited evidence of vaginal bleeding during the six-month observation period. Of these, thirteen patients (62%) experienced cessation of vaginal bleeding for an interval of at least 180 days while on study treatment and seven patients (33%) experienced cessation of bleeding for the duration of the trial (Figure3).